Remarks

Claims 1-369 were pending in the application. Claims 161-208, 257-304, and 362-369 have been canceled above, without prejudice, as drawn to a non-elected invention. Upon entry of this amendment, claims 1-160, 209-256, and 305-361 will be pending before the Examiner.

Applicants gratefully note the Examiner's acknowledgment and consideration of the Information Disclosure Statements of record.

Claims 1-160, 209-256, and 305-361 stand rejected as obvious over Richheimer *et al.*, in view of the September 1983 NCI report for Taxol. Applicants respectfully traverse. Applicants initially note that the primary reference was considered and is of record in all four of the patents which have issued from ancestral applications having identical disclosure to the subject application. Further, the claims in those patents are in some instances broader than those currently pending. Accordingly, Applicants respectfully assert that the U.S. Patent Office has already determined that Richheimer *et al.* is not sufficient to render the claimed invention obvious.

To support an obviousness rejection under §103, one must find both the suggestion, and the expectation of success, in the prior art. See *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Here, one finds neither. In fact, the only suggestion to create a pharmaceutical paclitaxel composition comprising paclitaxel, polyethoxylated castor oil, and an acid is found in the subject specification. As explained in more detail below, the only motivation to combine the references as asserted in the Office Action was provided by the Applicants' own discoveries and disclosures. Such "hindsight reconstruction" is improper.

One aspect of Applicants' claimed invention is the fact that they discovered that the standard paclitaxel formulation in 50/50 Cremaphor (polyethoxylated castor oil)/absolute ethanol was unstable if not kept refrigerated. The 1983 NCI clinical brochure (the secondary reference) states on page 4 that ampules should be refrigerated to 2-8° C, and adds that "*shelf-life surveillance of the ampule product is on-going*". Nine years later, in the NCI 1991 clinical brochure, the assertion is again repeated at page 4 that "*shelf-life surveillance of the ampules and vials is on-going*", while also stating at lines 3 and 4 of page 5 that **"Cremaphor EL does not alter the stability or activity of taxol"**. Nothing here teaches that the standard paclitaxel formulation has a stability problem. The primary reference, Richheimer *et al.*, is a study that saw instability in some paclitaxel standards that had been made up in methanol (page 325, column 2, lines 3 *et seq.*). Richheimer *et al.* has nothing to do with solutions of paclitaxel dissolved in polyethoxylated castor oil. In contrast to

polyethoxylated castor oil, which the 1991 NCI taxol brochure taught "does not alter the stability or activity of taxol" (page 5, lines 3 and 4, emphasis added), methanol is known to be quite nucleophilic, meaning that it is quite reactive, and reactivity of paclitaxel in methanol would not be unexpected. Methanol, of course, has no value at all as a solvent for clinical usage and is not found in any pharmaceutical paclitaxel composition. Richheimer *et al.* does not suggest that paclitaxel is unstable in basic environments generally, does not suggest that a Cremaphor solution of paclitaxel is basic or that a basic solution of paclitaxel in Cremaphor is one in which the paclitaxel would be unstable, and provides no suggestion whatsoever that adding acid to a paclitaxel solution in polyethoxylated castor oil would have any purpose in terms of paclitaxel stability. The secondary reference, the 1983 NCI taxol report, fails to cure these deficiencies.

Richheimer *et al.* has nothing to do with paclitaxel stability in pharmaceutical formulations, which is a problem each of the claims addresses. Rather, Richheimer *et al.* teaches the existence of paclitaxel and the results of experiments designed to induce reactions involving the paclitaxel molecule. As such, it teaches nothing about paclitaxel in polyethoxylated castor oil. As noted above, a comparison of the teachings of the 1983 NCI clinical brochure and the 1991 NCI clinical brochure shows that over a period of 8 years during which "shelf-life surveillance of the ampule product is on-going" the problem of paclitaxel instability in pharmaceutical formulations still had not been recognized. Applicants recognized this problem, and have taught a solution to the problem. Each of the claims has as an element the requirement that at least 96.6% of the paclitaxel potency is retained when the composition is stored at 40° C for seven days. This element is nowhere suggested or taught in either of the cited references. There has been no showing that the ordinary artisan as of the priority date was aware of any problem of paclitaxel instability in pharmaceutical formulations such as the storage form of paclitaxel in the NCI polyethoxylated castor oil/ethanol solution. The ordinary artisan therefore could not possibly have known to add acid to such formulations to improve the paclitaxel stability, and particularly in such a way as to meet the express limitations of the pending claims. Accordingly, there being no suggestion of the claimed invention in the prior art, no *prima facie* case of obviousness has been set forth. Reconsideration is respectfully requested.

In view of the foregoing, Applicants believe that all claims as currently pending are in condition for allowance and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this amendment, or if the Examiner believes that a telephone interview would expedite prosecution of the subject application to completion.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

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